III.
2 k Skin and Subcutaneous Tissue

To the most frequent changes in the area of the skin belonged inflammable processes, particularly phlegmons and abscesses (chart 84). Their frequency was influenced neith by the smoke-treatment nor by manipulations in the smoke-treatment apparatus. Occasionally, we observed eczemas and alopecia.

The spontaneous tumor frequency in the area of the skin was insignificant, see chapte III/2 m and chart 97. We observed:

I pavement epithelium carcinoma with strong keratizing and metastases,
I basalioma, (ill. 56)
nevi (in parts subcutaneous tissue of the eye region),
malignant, metastasizing melanomas, (ill. 57 and 58) hemangiomas,
I cystadenopapilloma, (ill. 59)
I neurinoma,
I clear-cell adenoma,
I skin papilloma

The skin carcinoma, the basalioma, the cavernous hemangioma and the neurinoma showed a histological structure comparable to that of a human tumor. The melanomas show a very strong pigmentation and mostly spindle-shaped regular cells and resemble, for the most parts, the so-called blue nevi in man. The malignant melanomas show two types of cells with more spindly cells and much pigment and more round cells with less pigment.

The cystadenopapilloma, which we found, resembles tumors of the same name described in the exocrine glands of man; its starting point was not precisely determinable.

Similar spontaneous skin tumors had been described already earlier by FORTNER (1957) among 620 hamsters 8 melanomas, FORTNER (1961) among 181 hamsters 5 melanomas, DUNHAM and HERROLD (1962) among 360 hamsters I pavement epithelium carcinoma, KIRKMAN (1962) among 7200 hamsters I neurofibroma, 21 blue nevi and 7 malignant melanomas and TOTH (1967) among 200 hamsters I melanocytoma. Melanomas and nevi were also described by

CRABB and KELSALL (1952), FORTNER and GALE (1958), GREENE (1958), SHUBIK, PIETRA and DELLA PORTA (1960), SCHRÖDER (1961), BOMIRSKI and Assoc. (1962) and RAPPAPORT and Assoc. (1963). LINDT (1958) reported of one basal cell carcinoma and one pavement epithelium carcinoma. They belong to the most frequent spontaneous tumors of the hamster.

After local and intravenous treatment with DMBA, different skin tumors (hemangiomas, melanomas, papillomas, carcinomas, sebaceous gland adenomas, adenocanthomas, cystadenomas, sarcomas) were described: KRIEGEL (1954), DELLA PORTA and Assoc. (1956), HORNING (1958), SHUBIK and Assoc. (1960), RAPPAPORT and Assoc. (1961), LEE and Assoc. (1963), HALNER (1966), TOTH (1969), RAITSCHEW (1970) and numerous others.

An increase in the tumors of the connective and supportive tissue, respectively the skin through the treatment was not provable (see also chapter: "Tumors of the Connective and Supportive Tissue").

III.

2 1 Tumors of the Suprarenal Gland

Among the relatively rare spontaneous tumors of the hamster, the relatively high frequency of suprarenal gland tumors had already been recognized early.

ASHBEL (I945) saw among I000 hamsters I0 suprarenal gland tumors, FORTNER (I957, I958) among 620 hamsters a total of I2I tumors(carcinomas, adenomas), FORTNER (I96I) among I8I hamsters 53 adenomas and I2 carcinomas, KIRKMAN (I962) among 7200 hamsters 550 adenomas and 3I adenocarcinomas, I ganglioneuroma (cortex), LEE and Assoc. (I963) among 54 hamsters 4 adenomas, SICHUK and Assoc. (I966) among 79 hamsters I7 adenomas, DUNHAM and HERROLD (I962) among 360 hamsters 6 carcinomas and frequently hyperplasias, TOTH (I967) among 200 hamsters 2 adenomas and 2 carcinomas, KIRKMAN (I950) among 5I hamsters 4 adenomas, FORTNER and GALE (I958) 2 carcinomas (number of animals not stated).

HOMBURGER and RUSSFIELD (I970) described in a new in-bred breed of Syrian Goldhamsters an occuring of suprarenal gland tumors provable up to 50 %. Thereby they distinguish essentially two types of kidney tumors, which they term A-B cell tumors and cortical tumors. The one form of tumors is described as more spindle-cellular while in the other roundly oval cells, that is, a tumor structure, respectively a cellular structure, respectively a structure of cells is being described which is more suggestive of the zona fasciculata of the suprarenal gland. The authors held genetic factors responsible for the formation of this high frequency of suprarenal gland tumors. The different tumor forms show, according to MURTHY and RUSSFIELD (I965 and I966) a very varied histochemical behavior and a varied hormonal effect.

We ourselves have distinguished between two forms of suprarenal gland tumors: spindle-cellular tumors (ill. 60) whose cell form and structure of cells is suggestive of the zona glomerulosa and

round-cellular (ill. 6I and 62) to oval cortex tumors which in their structure and their cell forms resemble more the zona fasciculata. The distinctly polymorphous adenoma forms show mostly a round-cellular, respectively a fasciculata resembling structure and were counted among these. This division does not contain a functional equating of the tumor with the morphologically similar cortex tissue. We observed in individual animals both tumor forms at the same time in the cortex of the suprarenal gland, and have not, like HOMBURGER and RUSSFIELD (I970), listed hyperplasias and adenomas separately, since, upon examination of larger series, we arrived at the conclusion that the adenomas develop from small cortical nodes which HOMBURGER and RUSSFIELD (I970) had termed hyperplasias

We termed only those tumors malignant which demonstrated an unequivocally infiltrative growing process into the neighboring areas and showed metastases (ill.63 a and b). In the evaluation of the examinations, we were interested in the sexual distribution of the tumors, the age dependency and the dependence on the nature of the treatment. Large tumors reached weights to above 2 g. Smaller tumors were not distinguishable from the weight of the suprarenal gland. With larger tumors, we found in the not-affected suprarenal gland a, to some extent, unequivocally provable compensatory atrophy. This becomes very clearly evident in a compilation (chart 85) in which appeared, in parts, one-sided tumors, and, in parts, two-sided tumors, whereby individual tumor-free suprarenal glands demonstrated a reduction of their weight to approximately I/4 of the average weight. Benign suprarenal gland tumors also showed an often considerable polymorphy of the nuclei. A correlation between amyloidosis and appearance of suprarenal gland tumors was not provable.

The frequency of suprarenal gland tumors (chart 86) was considerably lower in the female animals, a finding which was equally provable in the treated animals and the controls. We observed: benign tumors of the cortex (spindle-cellular) in females 3, in males 146; benign tumors of the cortex (round-cellular): in females 73, in males 340; malignant tumors of the cortex: in females I, in males 5. The differences are highly significant.

For the round-cellular tumors of the males, there are also highly significant differences between the groups 3, 4, 5 and 6 (X^2=23.I8; 3 FG) in the sense of a smaller frequency in the smoke-exposed animals. These differences are lacking for the spindle-cellular tumors. The round-cellular fasciculata resembling tumors of the suprarenal gland were more frequent than the spindle-cellular tumors of the suprarenal gland (4I3 : I49). A positive correlation resulted between the appearance of suprarenal gland tumors and the identification of a testicle atrophy. Whether this correlation is a case of a direct dependency or of a so-called pseudo-correlation, which is, in this

instance, attributable to the survival period with which both disease frequencies are highly correlated, remains to be seen.

An increase of the suprarenal gland tumors in the smoke-exposed animals was not provable.

Charts 87 - 96 show the age dependancy of the suprarenal gland tumors. We determined and listed in the chart for each group the number and the percentage rate of animals with tumors (spindle-cellular, round-cellular and malignant tumors of the cortex) in the 5 age groups (0-25, 26-50, 5I-75, 76-I00, > I00 weeks). A distinct age dependency becomes evident. While in the age group 0-25 weeks no tumors appeared at all, and in the age group 26-50 weeks tumors occured only very rarely, the tumor rate (in males) in the age group over I00 weeks often runs higher than 50 %.

Twice (groups I and I3, that is, not smoke-exposed animals) we found adenomatous growth of the marrow with cyst formation of the regular cells. The cysts were filled with secretion, the adenomas, which we termed cystadenomas, were very small. Similar tumors had been described earlier by SHRADER (I946), KIRKMAN (I962), KESTERSON and CARLTON (I970), and are extremely rare in relation to the cortex tumors.

Marrow-hyperplasias of the suprarenal gland or tumors, as STAEMMLER (I935) and ERMINKO (I955) observed them after chronic nicotine treatment in rats or cigarette smoke-condensate injections (MOHR and Assoc. I969), could not be proven by us.

III.
2 m Tumors of the Connective and Supportive Tissue

The observed tumors are compiled in chart 97 together with the tumors of the skin. The frequency of the sarcomas is unequivocally higher in the male animals.

The histological structure of the tumors (ill. 64 a - e) corresponds to the WHO classification for tumors in man. The total frequency of tumors is vastly in accord with former observations on the spontaneous frequency of sarcomas in the hamster:

FORTNER and GALE (I958)	among 620 = 6
FORTNER (I96I)	I8I = 2
KIRKMAN (I962)	7200 = 5
SICHUK and Assoc. (I966)	79 = 2
DUNHAM and HERROLD (I962)	360 = I
ASHBEL (I945)	I000 = 2
POPP, PREDETEANU (I960)	500 = I

Varied sarcomas of the connective and supportive tissues were also described by BUSCH (I953), CRABB and KELSALL (I954), KLEIN (I96I), LEE, TOTH and SHUBIK (I963), GRAUBMANN (I967), PATTERSON (I963), RUFFOLO and KIRKMAN (I965), GARCIA and Assoc. (I96I), FRIEDELL and Assoc. (I960), DELLA PORTA (I962), WEAVER (I952), LINDT (I958) GODGLUCK (I953).

Various sarcomas of the subcutaneous tissue were produced through local application of DEBA, (CHAUDHRY and Assoc. (I96I), CHAUDHRY and Assoc. (I96I), CHAUDHRY and Assoc. (I966), LEVY and RING (I950), LEE and Assoc. (I9 63), HOMBURGER and HSUEH (I970), RIVIERE and Assoc. (I963)).

Among the benign tumors, we would like to report on an odotoma (ill. 64 f), as a particularly remarkable case of a tumor, which had formed in the interior of the jaw-bone and showed epithelial and mesenchymal components. The tumor showed solid substances, respectively differentiation products in the sense of future tooth components.

III.
2 n Malignant New Formations of the Hematopoietic, respectively the Lymphoreticular Tissue.

To the spontaneous tumors of the goldhamster belong the tumors of the hematogenic and/or lymphoreticular tissue as some of the most frequently observed. FORTNER (I957 and I958) found among 620 hamsters I9 lymphosarcomas, STRAULI and HAMMERLI (I960) among 50 hamsters 5 lymphosarcomas, FORTNER (I96I) among I8I hamsters 5 reticulo cell sarcoma and I plasmocytoma, KIRKMAN (I962) among 7200 hamsters 2 reticulosarcomas and I plasmocytoma, STRAULI (I962) among 500 hamsters 32 reticulosarcomas, DUNHAM and HERROLD (I962) among 360 hamsters I2 reticulosarcomas, 3 plasmocytomas and 4 "lymphocytic tumors", HORN and SIEWERT (I968) among 760 hamsters 5 lymphosarcomas, respectively among I630 hamsters 30 lymphosarcomas. Malignant lymphomas were found by TOMATIS and Assoc. (I96I) (2 among 40 hamsters) as well as TOTH (I967) (9 among 200 hamsters). In a compilation by SHUBIK and Assoc. (I962), the frequency of malignant lymphomas in the controls is listed as I.3 % (= 549 animals). Besides that, individual observations of reticulosarcomas, plasmocytomas or lymphosarcomas were reported(FORTNER and GALE I958, HANDLER and Assoc. I960, BRINDLEY and BANFIELD I96I, GARCIA and Assoc. I96I, LUCAS I96I, and RIVIERE and Assoc. I96I).

Conspicuous is the rare observation of leukemias. One case each were described by LINDT (I958), KIRKMAN (I962) and by HORN and SIEWERT (I968). Lymphatic leukemias were described in the hamster by GRAFFI (I97I) after infection of Papova-Virus.

After chronic treatment with DMBA, RAPPAPORT and Assoc. (I96I) saw in I of 24 hamsters, LEE and Assoc. (I963) in one of 53 hamsters and TOTH (I969) in I7 of 60, respectively 8 of 59 hamsters, malignant lymphomas. In a compilation by SHUBIK and Assoc. (I962), the frequency of malignant lymphomas, upon DMBA-treatment of the skin, is listed with 2.9 % (= I02 animals), while after oral treatment with 2-acetaminofluorene I.I %, with urethane 7.4 %, with 20-methylcholanthrene 7.0 % and with O-aminoazotoluene 6.7 % of the hamsters showed malignant new formations.

Somewhat confusing is the histological classification of the observed tumors which was undertaken by the individual authors under very varying points of view. We set up the following classification (ill. 65 a - h)* for the observed malignant new formations of the hematopoietic, respectively the lymphoreticular tissue:

	macroscopically	microscopically
Leukemias lymphatic:	enlargement of liver, spleen and lymph nodes	in the liver predominantly periportal infiltrates of small lymphoid cells. Diffuse infiltration, for instance, of the lymph nodes, spleen etc.
myelonic:	enlargement predominantly of the liver, to a lesser extent than of the lymph nodes and the spleen	in parts, extreme diffuse infiltration of the liver with stron dissoziation, in parts, dense infiltration of lymph nodes and bone-marrow. Positive chloracetate-esterase reaction.
Lymphosarcomas type I:	in parts, diffuse, in parts, nodular enlargement, predominantly of lymph nodes, liver, spleen, bone-marrow. Metastases also in kidney, skin, myocardium and other organs	medium-size strongly basophile cells. Negative chloracetate-esterase reaction, vastly uniform lymphoid cell type.
Type II:	as type I	medium-size, strongly basophile cells. Negative chloracetate-esterase reaction. In between embedded are small round cells, particularly in tumors with strong bone-marrow displacement, in the liver myelopoiesis foci with positive chloracetate esterase reaction.
Type III;	as type I	large-cellular tumor with strongly basophile cells which resemble reticulum cells. Uniform cell type without small round cells. No myelopoiesis, no chloracetate-esterase reaction. Histological structure largely comparable to the reticulosarcoma in man.

* We thank Prof. Dr. Lennert, Director of the Pathological Institute of the University of Kiel for his assistance in classifying the preparations.

	macroscopically	microscopically
Myelosarcoma	diffuse to nodular infiltration of the organs	in parts, tumor-nodes from large basophile cells with broad cytoplasma. Profusely latticed fibers. Tumor cells with several nuclei. In tumor-nodes, in liver and spleen, foci of myelopoiesis with segmental nuclei cells, which show, in parts, a positive, in parts, a negative chloracetat esterase reaction. In liver and spleen abundantly polymorphous megacaryocites.
Plasmocytoma	in parts, individual tumor-nodes, in parts, diffuse and nodular infiltration of the organs	nearly pure cultures of plasma cells with typical structure and, in parts, distinct, in parts, minor polymorphy. In the liver here and there copious plasmacells in the capillaries (plasmacell leukemia ?)

The difficulaties in the delimitation between lymphosarcoma reticulasarcoma and myelosarcoma shall not be discussed in detail in this context. However, we would like to point out that the general term lymphosarcoma does not exclude the possibility of a myelogenetic origin of individual tumors. The delimitation between tumor and leukemia was also often difficult since we did not have blood-counts, for the animals which, without exception, all died spontaneously. Therefore, we regarde for instance, extramedullary myelopoiesis in the liver with lymphosarcomas of type II as compensatory hematogenesis with strong marrow displacement through tumor cells.

In the comparison of the test results between the different animal groups, we summed up the total number of available malignant new formations of the hematopoietic, respectively the lymphoreticular tissue, that is, leukemias and tumors were counted together, since a sharp differentiation between tumor and leukemia was often not possible, and because this summation was considered reasonable for the total evaluation of the test.

A correlation between the nature of the treatment of the test animals and the frequency of the appearance of tumors of the lymphoreticular and hematopoietic system is not recognizable (chart 98). However, in the animals of groups I and 2, treated with DMBA, a significantly earlier appearance of these changes is found, as compared to the controls as well as the animals only exposed to smoke.